REMARKS

I. Status of the Claims

Claims 15-17, 22-26, 31-34 and 52 are pending. Claims 1-14, 18-21, 27-30, and 35-51 were previously canceled without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications to the canceled subject matter.

Claim 15 has been amended to clarify that which Applicants consider to be one aspect of their invention. The claim requires using a particle-mediated transdermal delivery technique to administer core carriers that are coated with HSV genetic fragment(s) to a subject. According to the claim, a vector construct, e.g., a plasmid or a cosmid, carries an HSV genomic DNA fragment(s), which expresses only the HSV immediate early genes ICP 27, ICP 0, ICP 4 and ICP 22. Those four immediate early genes are expressed in an amount sufficient to elicit an immune response in the subject. The HSV genomic fragment or fragments, which contain those four genes, is, collectively, between about 5 kilobases and about 25 kilobases in size.

These amendments do not introduce any new matter. Applicants have deleted the "non-overlapping" terminology from claim 15, simply to expedite prosecution; and not in acquiescence with the Office's position that that particular term introduces new matter. Accordingly, the new matter rejection (page 2) and the rejection under 35 U.S.C. § 112, first paragraph (page 3) are moot.

II. Response to Issues Raised by Examiner in Outstanding Office Action

a. Claim Rejections - 35 U.S.C. § 103

The Examiner says that even if the term "non-overlapping" is deleted from claim 15, claims 15-20, 22-29 and 31-34 would still be unpatentable under 35 U.S.C. § 103 as allegedly obvious over Suter *et al.* (Vaccine 1999, Vol. 96, No. 22, pp. 12697-13702) in view of Hilliard et al. (Arch Virol. 1989, Vol. 109, No. 102, pp. 83-102). The Examiner asserts that although the viral genome of Suter *et al.* is much larger than the 50 kilobases upper limit specified by the claims, it would have been obvious to a person with ordinary skill in the art to use the much smaller genomic fragments employed in the present invention, because Suter

et al. already approve that a viral genome lacking a small region is able to induce an immune response as a DNA vaccine. Applicants respectfully disagree and request reconsideration and withdrawal of the rejection.

Claims 18-20 and 27-29 have been cancelled. Therefore, the rejection of these claims is moot.

The combined teachings of Suter *et al.* and Hilliard et al. fail to teach or suggest all of the limitations of the claimed invention, as amended. Suter *et al.* fails to teach or suggest the claimed invention because the only region of the HSV genome deleted in Suter *et al.* are the non-coding packaging signals, meaning that the viral genome contains all of the normal coding sequences of the virus. The viral genome employed in Suter *et al* is therefore far larger, at 150 kb, and expresses all of the possible HSV coding sequences, in direct comparison to the genomic nucleic acid fragments employed in the present invention, which have a maximum size of a third of the length of the viral genome employed in Suter *et al* and express only four ICP antigens.

The thrust of Suter *et al.* is to express all of the viral proteins to as closely mimic viral infection as possible. This is highlighted at page 12702, left hand column, final paragraph of Suter *et al.*, where it is stated that:

> "*The prototype BAC-VAC described in this report contains a 150-kb modified HSV-1 genome that is replication competent in mammalian cells and expresses at least all of the 36 viral genes that are essential for HSV-1 replication, but does not produce infection progeny virus.*" [emphasis added]

This is also evident from the abstract of Suter *et al.* which states that:

> "*A safe modification of fHSV, fHSVΔpac, does not give rise to progeny virus because the signals necessary to package DNA into virions have been excluded. However, in mammalian cells fHSVΔpac DNA can still replicate, express the HSV-1 genes, cause cytotoxic effects, and produce virus-like particles. Because these*

functions mimic the lytic cycle of the HSV-1 infection, fHSVΔpac was expected to sttimulate the immune system as efficiently as a modified live virus vaccines"

It would be counterintuitive from the teaching of Suter *et al* for the skilled person to reduce the size of the fHSVΔ pac construct by two-thirds and delete large numbers of genes. Such an approach would be contrary to the teaching of Suter *et al.* which aims to mimic infection as closely as possible and express as many of the normal viral proteins in order to achieve that aim. That is also evident from Suter *et al* at page 12967, in the paragraph bridging the left and right hand columns, which again stresses the importance of expressing as wide a range as possible of antigens.

As highlighted at page 19, lines 29 to page 20, line 2 of the present application expressing all of the genes of a virus is a undesirable because some viral proteins can inhibit immune responses and/or be immunodominant decreasing the chances of eliciting a protective immune response. The vector construct of the present invention expresses a subset of HSV antigens, namely ICP 27, ICP 0, ICP 4 and ICP 22, and hence avoids such problems. Suter *et al* contains no appreciation of the value of expressing only a subset of the proteins of HSV.

In particular, in direct contrast Suter *et al.* directs the use of a construct to express as many of the viral proteins as possible. Therefore, Suter *et al.* teaches away from the present invention which employs much smaller regions that express the desired ICP antigens in their natural context. Unlike the viral genome, which has only a small deletion, employed in Suter *et al*, the constructs of the present invention express a smaller, defined subset of antigens in the ICP antigens and are not intended to cause cytopathic effects and produce virus-like particles. Indeed they do not comprise enough of the genome of the pathogen, or express enough of the proteins of HSV, to be able to do so.

The present claims refer to size ranges for the fragments of from 5 to 25 kb for a plasmid and 25 to 50 kb for a cosmid, which is a third or less of the 150 kb HSV genome. Since the claimed constructs carry a third or less of the HSV genome, they are distinct from the construct in Suter *et al.* which carries virtually all of the HSV genome. As discussed

above, the crux of Suter *et al* is to express as many of the HSV antigens as possible and hence teaches in the opposite direction to the vector construct now specified by the claims which expresses only four ICP antigens.

The Examiner's attention is also drawn to Example 1 of the present application, and in particular to page 46, lines 6 to 16, which indicates that the immune response seen with the constructs of the present invention comprising genomic fragments is unexpectedly superior to that seen with a plasmid comprising only the antigen coding sequences and none of the accompanying genomic sequences. Thus, not only do the constructs of the invention not suffer from the problems of viral vectors that express all of the proteins of a virus, but they are also superior to vectors which express isolated antigen coding sequences.

It is also highlighted, that even if the skilled person did, for any reason, consider deleting any further sequences from the viral genome discussed in Suter *et al* they would still not arrive at the viral construct specified by the claims which expresses only the ICP 27, ICP 0, ICP 4 and ICP 22 genes. Suter *et al* does not mention the ICP antigens. Thus, even if the skilled person were to start deleting sequences from the construct of Suter *et al.*, there is no reason why they would specifically retain the sequences encoding the ICP antigens and delete coding sequences for other antigens. Neither Suter *et al* or indeed Hilliard *et al* teaches or suggests the limitation of specifically retaining the coding sequences for the four ICP antigens so that the resulting construct only expresses those antigens. As such the subject matter of the claims is also non-obvious over Suter *et al* for that reason.

The teachings of Hilliard *et al.* do not cure the deficiencies of Suter *et al.* Hiliard *et al* is simply a review of Herpes viruses, does not comment on the generation of constructs and does not mention the ICP antigens. Therefore, the claimed invention is not obvious over the combined teachings of Suter *et al.* and Hilliard *et al.*

b. Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 15-20, 22-29, 31-34, and 52 are rejected by the Examiner under 35 U.S.C. § 112, first paragraph for lack of written description. The Examiner asserts that Applicants "only disclose to use a DNA vector as a DNA vaccine for eliciting an immune response,

Applicants do not have a possession for more than one vectors to delivery more than one pathogens DNA fragments." Office action at page 4.

Applicants do not acquiesce with this position, but have clarified claim 15 to make clear that the claimed method requires "administering core carriers coated with a vector." Accordingly, Applicants respectfully request that this rejection be withdrawn.

III. Conclusion

Applicants believe that the present application is now in condition for allowance and respectfully request favorable reconsideration of the application. Applicants invite the Examiner to contact the undersigned by telephone if it is felt that a telephone interview would advance prosecution.

In this regard, if Examiner Li believes that this paper does not place the claims in condition for allowance, then the undersigned requests an interview with her and her supervisor. The undersigned believes that the courtesy of an interview is appropriate in view of the unavailability of the Examiner's supervisor to conduct an interview prior to the August 23rd due date.

Respectfully submitted,

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